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REISSUE PATENT APPLICATION TRANSMITTAL

Address to: Assistant Commissioner for Patents Box Patent Application Washington, DC 20231	Attorney Docket No.	70869-0078
	First Named Inventor	Wells
	Original Patent Number	5,707,331
	Original Patent Issue Date (Month/Day/Year)	January 13, 1998
	Express Mail Label No.	

APPLICATION FOR REISSUE OF: ☒ Utility Patent ☐ Design Patent ☐ Plant Patent
(check applicable box)

APPLICATION ELEMENTS	ACCOMPANYING APPLICATION PARTS
1. <input checked="" type="checkbox"/> * Fee Transmittal Form (PTO/SB/56) (Submit an original, and a duplicate for fee processing)	7. <input type="checkbox"/> Foreign Priority Claim (35 U.S.C. 119) (if applicable)
2. <input checked="" type="checkbox"/> Specification and Claims (amended, if appropriate)	8. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations
3. <input checked="" type="checkbox"/> Drawing(s) (proposed amendments, if appropriate)	9. <input type="checkbox"/> English Translation of Reissue Oath/Declaration (if applicable)
4. <input checked="" type="checkbox"/> Reissue Oath / Declaration (original or copy) (37 C.F.R. § 1.175)(PTO/SB/51 or 52)	10. <input type="checkbox"/> * Small Entity Statement(s) <input checked="" type="checkbox"/> Statement filed in prior application, Status still proper and desired (PTO/SB/09-12)
5. Original U.S. Patent <input type="checkbox"/> Offer to Surrender Original Patent (37 C.F.R. § 1.178) (PTO/SB/53 or PTO/SB/54) or <input type="checkbox"/> Ribboned Original Patent Grant <input type="checkbox"/> Affidavit / Declaration of Loss (PTO/SB/55)	11. <input type="checkbox"/> Preliminary Amendment
6. Original U.S. Patent currently assigned? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (If Yes, check applicable box(es)) <input type="checkbox"/> Written Consent of all Assignees (PTO/SB/53 or 54) <input type="checkbox"/> 37 C.F.R. § 3.73(b) Statement <input type="checkbox"/> Power of Attorney	12. <input checked="" type="checkbox"/> Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
	13. <input type="checkbox"/> Other:

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TECHNICAL FIELD

BACKGROUND

U.S. Pat. No. 5,178,602 (Wells) and U.S. Pat. No. 5,047,004 (Wells) show an automated centrifuge, which includes structure for holding a centrifuge tube, after centrifugation, in a position that allows the supernatant to drain from the tube and into another container by gravity. The holding structure shown in these patents comprises a locking mechanism mounted for axial movement with respect to the axis of rotation of the centrifuge. An electromagnet that is easily controlled causes the axial movement.

It is also known to decant a supernatant by the process of centrifugal draining. According to that process, a centrifuge rotates a centrifuge tube while the tube is held in a position such that the supernatant is drained from the tube by centrifugal forces.

Fibrin sealants for treating wounds are known and are typically produced by combining a fibrinogen/Factor XIII component with bovine thrombin. When these are mixed, a fibrin tissue adhesive results, which is applied to the wound. Descriptions of compositions for use as tissue sealants are given in U.S. Pat. No. 5,292,362 and U.S. Pat. No. 5,209,776 (Bass et al.). The fibrinogen is obtained from plasma, either pooled or autologous, and cryoprecipitation is one known technique for separating fibrinogen from plasma. One cryoprecipitation technique is described in U.S. Pat. No. 5,318,524 and includes the centrifugation of thawing plasma to produce a precipitate containing fibrinogen/Factor XIII. Other techniques for producing fibrinogen/Factor XIII include inducing precipitation of the component by addition of such agents as Ammonium Sulfate or polyethylene glycol (PEG) to blood plasma.

Several known chemical procedures include repeated steps of physical separation between two or more components. Separation based on density differences between the components is often by centrifugation, and the resulting supernatant is decanted to complete the separation. Each step provides an opportunity for error, which would be reduced by automation of the process.

In accordance with the invention, chemical procedures requiring several centrifugation steps are automated, to reduce the time required by a clinician and eliminate the potential for errors. Apparatus in accordance with the invention includes a multiple-chamber container and a centrifuge designed to receive the container and subject its contents to predetermined centrifugation steps as well as gravity and centrifugal decanting of the supernatant.

In accordance with this embodiment of the invention, a patient's anticoagulated blood is placed in the first chamber of the disposable container, and a precipitation agent is placed in the second of the chambers. The container is then placed in the swinging frame of the centrifuge, and the control circuit is activated to initiate the operation of the centrifuge. The centrifuge first rotates the container for a time period that has been determined to be adequate for separating the cellular components from the supernatant plasma. During this time, the swinging frame will have rotated outwardly substantially due to centrifugal forces on the container. While the frame is in the outwardly rotated position, the locking means is activated to lock it there. The rotation of the support is then terminated. As the rotational velocity of the support decreases, the supernatant fluid, being no longer subject to the centrifugal forces, flows out of the first chamber and into the second chamber by gravity. The cellular component is more viscous and, thus, flows toward the second chamber at a rate less than that of the plasma. Preferably, however, a divider in the form of a disk is placed in the first chamber to restrict the flow of the cellular components and plasma below the disk. The disk is at a depth that provides a predetermined volume of plasma, which is normally near the expected boundary between the

supernatant and cellular components. After a period of time that has been determined to allow an adequate amount of the plasma to flow into the second chamber, the locking means is deactivated to release the container, whereby it assumes an upright position with the cellular component remaining in the first chamber and the plasma now in the second chamber. The rotatable support is then alternately activated and deactivated for short intervals to mix the plasma with the precipitating agent in the second chamber. Interaction between the precipitating agent and the plasma initiates precipitation of fibrinogen and Factor XIII from the plasma. The support is then again rotated to accelerate the precipitation of the fibrinogen/Factor XIII and to create a pellet in the bottom of the second chamber. As a final step, the locking means is again activated to lock the container in a position such that the supernatant resulting from precipitation of the fibrinogen is decanted by centrifugal draining into the first chamber. In this step, the container is held substantially upright, and the support is rotated to apply centrifugal forces to the supernatant, whereby it flows over the wall between the chambers and into the first chamber. The locking means is then inactivated, the container removed from the centrifuge, and the fibrinogen/Factor XIII removed from the second chamber for further processing. In a preferred embodiment, the fibrinogen/Factor XIII is reconstituted and then, combined with thrombin, and applied to a patient to treat a wound.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a perspective of a container and centrifuge in accordance with the invention.

FIG. 2 is a vertical cross section of a preferred embodiment of a container.

FIGS. 3a and 3b are partial vertical cross sections of the centrifuge of FIG. 1.

FIGS. 4a through 4f are schematic diagrams illustrating a preferred method of operation of the centrifuge of the invention.

DETAILED DESCRIPTION OF THE INVENTION

With reference to FIGS. 1 and 2 of the drawings, a centrifuge 2 is designed to receive a container 4 in accordance with the invention. The centrifuge is capable of subjecting the container to a series of steps that will be described in detail below. The container includes at least two chambers, 6 and 8. Chamber 6 is designed to receive a first fluid to be treated, such as blood. Chamber 8 is designed to receive fluids that have been decanted from chamber 6, such as a supernatant plasma resulting from centrifugation of blood in chamber 6.

A preferred form of the container is shown in detail in FIG. 2. As shown, the container comprises three primary parts. A base part is preferably molded and includes the chambers 6 and 8 and a bridge 7, which connects the two chambers. A lid 11, also preferably molded, fits over the tops of the chambers to close them. The lid includes cup shaped extensions 12 and 14, each of which is centrally aligned with a respective one of the chambers 6 and 8. Extension 12 has a access port in the form of centrally located opening 13, while extension 14 has a centrally located opening 15. The openings receive syringe needles to permit fluids to be injected into the chambers or withdrawn therefrom. Membranes 16 and 17 cover the openings 13 and 15 to maintain sterility. The membranes are preferably heat sealed into the extensions 12 and 14 during construction by providing a

cavity for receiving the membranes. After a membrane is inserted, the upper edges of the cavity are folded over and welded, e.g., ultrasonically, to retain the membrane.

The lid also includes a bridge 7 that cooperates with bridge 7 in the base to form a fluid channel 18, connecting chambers 6 and 8. As shown, the bridge 7 extends above the tops of the chambers 6 and 8 to prevent communication between the chambers by "splashing." Intentional fluid communication between the two chambers will be described in detail below.

A separation disk 20 is preferably placed in chamber 6 near, but always above, the expected vertical position of the boundary between supernatant plasma and cellular components after a first centrifugation of a blood sample. The hematocrit is known to vary among individuals, and the exact amount of plasma that will result from a blood sample cannot be accurately predicted without prior testing of the sample. Thus, disk 20 is located such that the plasma above the disk after centrifugation of a predetermined volume of blood is a predetermined volume of plasma. The upper surface of the disk 20 is tapered toward an edge, and the edge includes at least one groove 22 that allows fluid communication between the parts of the chamber 6 that are above and below the disk 20.

In a preferred embodiment, a cylindrical support 24 is attached to the lower surface of the disk to set the location of the disk during assembly.

A hollow tube 26 is provided to facilitate introduction of the blood sample to the portion of the chamber 6 that is below the disk 20. The tube 26 extends from just below the opening 13 through disk 20. Thus, a syringe needle inserted through opening 13 pierces membrane 16 and communicates with tube 26 to allow injection of the blood sample into the bottom of the chamber 6. The groove 22 permits downward movement of the plasma and cellular components during centrifugation but retards movement of the cellular components during decanting. Also, an air vent 27 is provided for chamber 8 to facilitate introduction and withdrawal of fluids.

In use, a container 4 is placed in a holder on the rotor of the centrifuge as indicated in FIG. 1. To balance the rotor, two such containers are preferably placed in the centrifuge in diametrically opposed positions. Of course, only one container may be used and a weight or "dummy" container used to balance the rotor.

FIGS. 3a and 3b are partial cross sections of a preferred embodiment of a centrifuge showing the container locked in two different positions. A rotor shaft 28 is connected to a motor (not shown), which rotates the shaft. A rotor 30 is mounted to the shaft for rotation and has a frame 32 pivotally mounted to the rotor 30 at pivot connection 34. The top surface (not shown) of the frame 32 has two circular openings for receiving the chambers 6 and 8 whereby the container can be placed in the frame such that the contents of the container will be subjected to centrifugal forces as the rotor is rotated. A bias spring 35 ensures that the frame 32 will pivot to an upright position when centrifugation is terminated. The frame 32 may also be shaped to reduce wind resistance, as known in the art.

A locking plate 36 is mounted coaxially with the shaft 28 for engaging the frame 32 to lock the container in desired orientations. The plate and the mechanism for controlling the positions of the plate may be the substantially the same as that shown in my previous U.S. Pat. No. 5,178,602. For example, an electromagnet 38 may be provided to control the position of the locking plate by action on a permanent magnet 40, which is attached to the locking plate.

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The automated process for production of fibrinogen is at this point complete, and the fibrinogen pellet is preferably

extracted from the container 8 by a syringe for further processing. For example, the fibrinogen may be reconstituted and combined with thrombin to produce a sealant or an adhesive.

The apparatus of the invention may be used for other automated processes. For example, another technique for the separation of fibrinogen from blood in accordance with the structure of the invention uses cryoprecipitation. According to this technique, plasma is frozen to a temperature of about minus 20° C., thawed, and then centrifuged to separate the fibrinogen from plasma. The multiple-decanting apparatus of this invention may be used to automate cryoprecipitation by inclusion of a temperature control device 50 in thermal contact with the centrifuge. The temperature control device may comprise any of several known structures, including liquid nitrogen or liquid oxygen based devices and refrigeration devices.

To effect automated cryoprecipitation, a sample of blood is placed in the first chamber 8, and the container is then placed in the centrifuge and subjected to a first centrifugation. The plasma is then drained into the second chamber 8, for example by gravity draining. The temperature control device is then activated first to freeze the plasma and then to allow the plasma to thaw. The thawed plasma is subjected to a second centrifugation, which separates fibrinogen from the remainder of the plasma. The supernatant plasma is then separated from the fibrinogen by draining it back into the first chamber, for example by centrifugal draining, whereby only fibrinogen remains in the second chamber. The container is then removed from the centrifuge, and the fibrinogen removed from it for use as described above. Of course, the freeze-thaw-centrifuge process may be carried out any number of times before the supernatant is drained back into the first chamber.

Modifications within the scope of the appended claims will be apparent to those of skill in the art.

We claim:

1. A centrifuge comprising means for removably receiving a unitary container having a plurality of chambers for receiving substances to be centrifuged, means for rotating said container to subject said substances to centrifugation, and means for locking said container in a first predetermined position to allow a supernatant in a first of said chambers to transfer into a second of said chambers and for locking said container in a second position to transfer a supernatant in said second chamber to another of said chambers.

2. Apparatus according to claim 1 wherein said means for locking, when activated, locks said container such that a supernatant in one of said chambers transfers into another of said chambers by gravity draining.

3. Apparatus according to claim 1 wherein said means for locking, when activated, locks said container such that a supernatant in one of said chambers transfers into another of said chambers by centrifugal transferring.

4. Apparatus according to claim 1 wherein said means for locking, when activated to a first position, locks said container such that a supernatant in said first chamber drains into said second chamber by gravity draining and, when activated to a second position, locks said container such that a supernatant in said second chamber transfers into said first chamber by centrifugal transferring.

5. Apparatus according to claim 1 wherein said locking means comprises a movable plate and means for controlling the position of said plate.

6. Apparatus according to claim 5 wherein means for controlling is electrical.

7. Apparatus according to claim 6 wherein said means for controlling is magnetic.

15. Apparatus according to claim 14 wherein said divider means includes a periphery having at least one groove therein for allowing fluid communication between said two parts.

21. A centrifuge comprising a first chamber for receiving a fluid substance and a second chamber for receiving a fluid substance, means for rotating said first and second chambers to subject said substances to centrifugation, and means for locking said chambers in first predetermined positions and for locking said chambers in second predetermined positions, means for transferring a supernatant in said first chamber into said second chamber by gravity when said chambers are in said first predetermined positions and for transferring a supernatant in said second chamber to said first chamber by centrifugal transfer when said chambers are in said second predetermined positions.

22. A system for treating physiological products, comprising:

a centrifuge;

a container having at least a first chamber and a second chamber, wherein each of the first and second chambers have a top portion, a bottom portion and a set of walls, wherein the top portions of the first chamber and second chamber are connected by a bridge for transferring fluid therebetween; and

a holder assembly attached to the centrifuge and effective to removably receive the container, wherein the holder assembly is effective to position the container in one or more predetermined positions.

23. The system of claim 22, wherein the chambers include removable lid portions, thereby forming a closed container.

24. The system of claim 23 wherein at least one of the chambers includes an access port for transference of a liquid.

25. A container comprising:

at least a first chamber having a top portion, a bottom portion and a first set of walls;

a second chamber having a second top portion, a second bottom portion and a second set of walls;

and a bridge connecting the top portion of the first chamber and the top portion of the second chamber, such that a substance can be transferred from the first chamber to the second chamber while the container is positioned at a predetermined angle.

26. The container of claim 25, wherein the chambers include a removable lid portion.

27. The container of claim 26, wherein at least one of the chambers includes an access port for transference of a liquid.

28. A system for treating physiological products and maintaining sterility of said products during said treating comprising:

a container having a plurality of closed, sterile fluid-receiving chambers, a bridge forming a fluid path

Abstract

[illegible]

- Abstract**

ABSTRACT

A centrifuge is capable of holding a sample container in selected orientations, either during or after centrifugation, to drain supernatants between two or more chambers of the container. The draining may be gravity or centrifugal draining. This allows an automated process to subject a sample to a first physical or chemical treatment to produce a first supernatant, the first supernatant to be subjected to a second physical or chemical treatment, and a second supernatant to be separated from a desired component.

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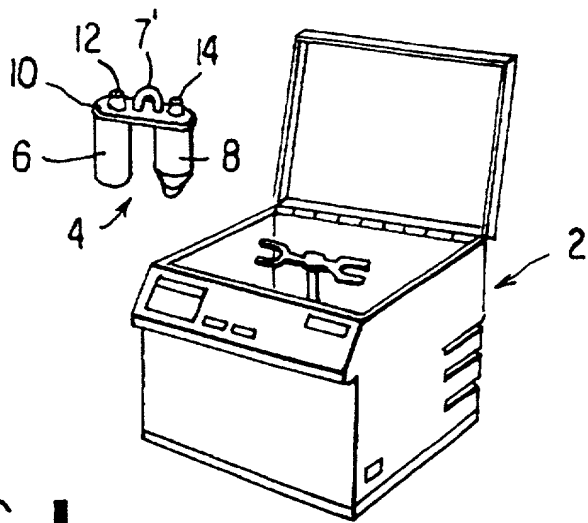


FIG. 1

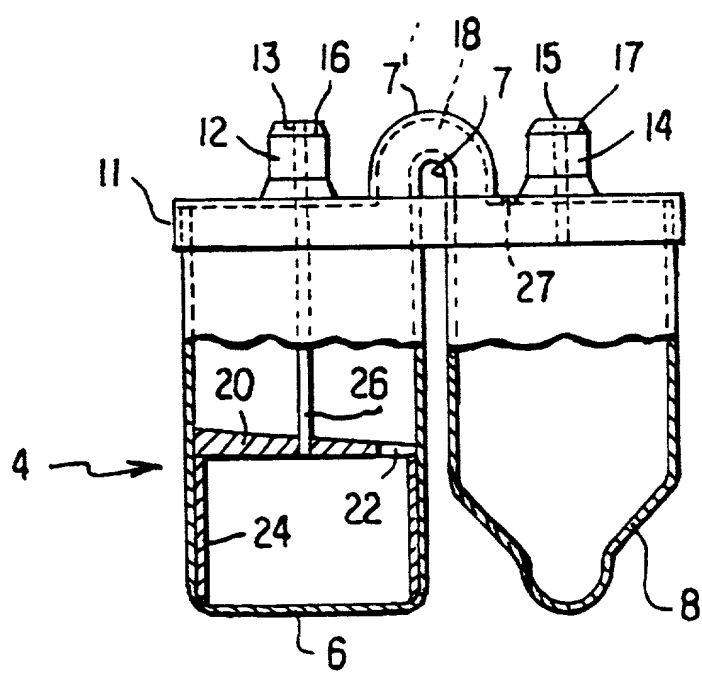


FIG. 2

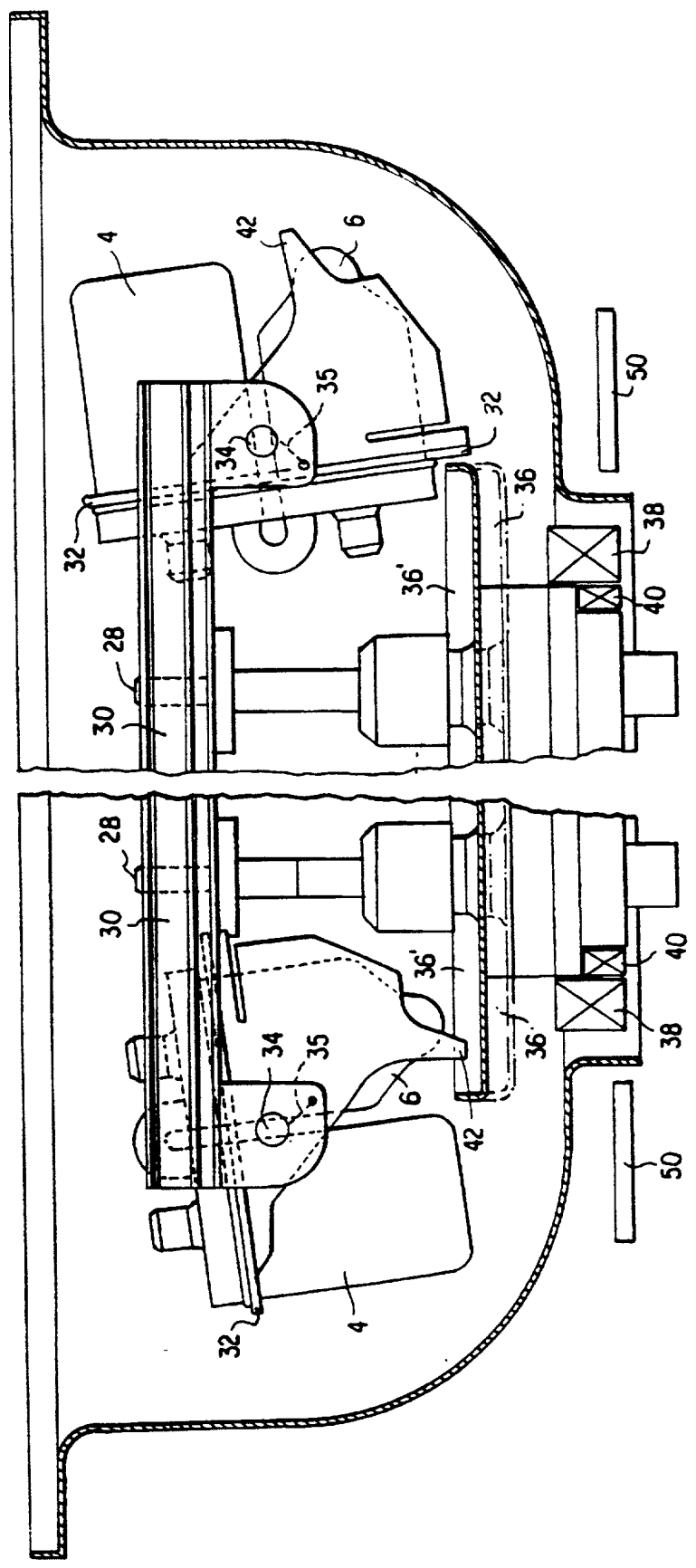


FIG. 3a

FIG. 3b

FIG. 4a

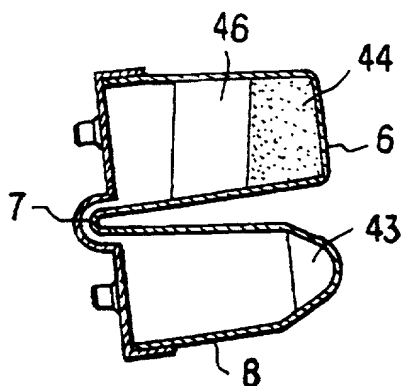


FIG. 4b

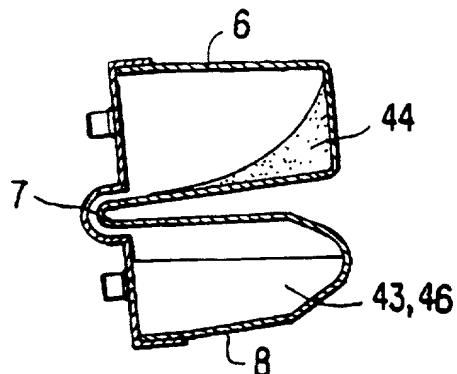


FIG. 4c

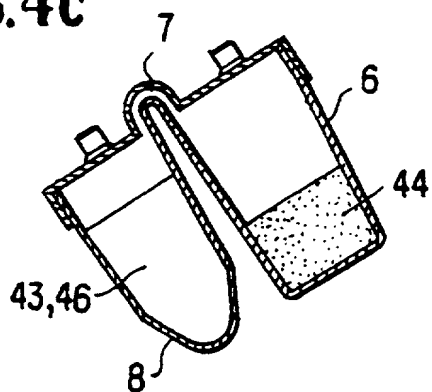


FIG. 4d

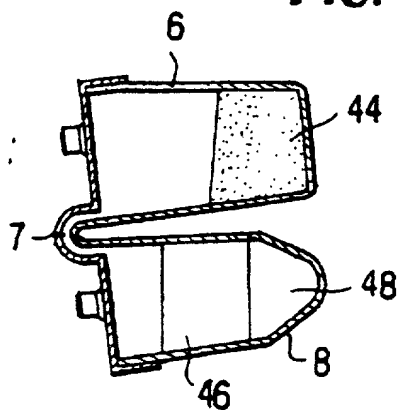


FIG. 4e

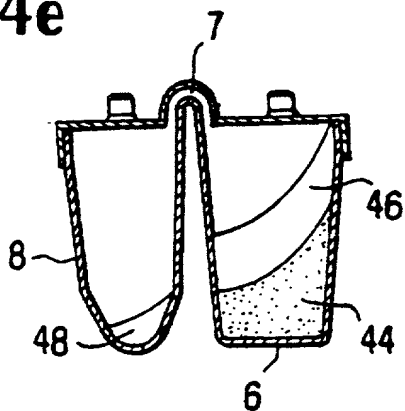
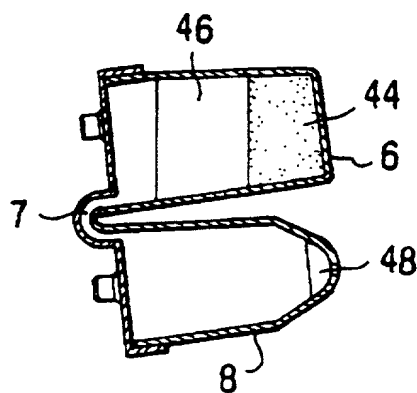


FIG. 4f



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :)
)
Wells et al.)
) Art Unit:
Serial No.: Reissue of 5,707,331)
) Examiner:
Filed: January 13, 2000)
)
For: AUTOMATIC MULTIPLE)
DECANTING CENTRIFUGE)

REISSUE DECLARATION AND POWER OF ATTORNEY

The undersigned applicants hereby declare as follows:

1. We believe the original patent to be partly inoperative or invalid by reason of our claiming less than we had the right to claim in the patent.
2. An error in the original patent was the failure to claim overlooked embodiments that provide treatment of physiological fluids in a centrifuge in such a manner that sterility of the fluids is maintained during treatment.
3. All errors that are being corrected in the present reissue application up to the time of filing this declaration arose without any deceptive intention on our part.
4. We have reviewed and understand the contents of the specification, including the claims, as amended by any amendment on _____.
5. We believe ourselves to be the original and first inventors of the subject matter claimed and for which a patent is sought.
6. We acknowledge the duty to disclose to the Office all information known to us to be material to patentability as defined in 37 CFR §1.56.

OFFICE OF THE COMMISSIONER OF PATENTS AND TRADEMARKS

7. All statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 USC §1001 and that such willful false statements may jeopardize the validity of the application, and patent issued thereon, or any patent to which this declaration is directed.
8. We hereby appoint Conrad J. Clark (Reg. No. 30, 340) and Christopher W. Brody (Reg. No. 33,613) as our attorneys to prosecute this application, with full powers of substitution. Please send all correspondence to:

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by: Lynn A. Jakary, Executrix
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Residence: _____
Date: _____

Steven M. Gann

Post Office Address: _____
Residence: _____
Date: _____